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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/075,490 | 02/12/2002 | Julie A. Johnson | UF-265CXC1 | 8778 |

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| EXAMINER | |
|---|---|
| FREDMAN, JEFFREY NORMAN | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1634 | |

DATE MAILED: 01/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/075,490 | JOHNSON, JULIE A. | |
| | Examiner | Art Unit | |
| | Jeffrey Fredman | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *15 December 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3 and 9-16* is/are pending in the application.

4a) Of the above claim(s) *14-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3 and 9-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

### *Election/Restrictions*

1. Newly submitted claims 14-16 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: These claims are directed towards methods of treatment, not methods of predicting responsiveness. These claims utilize different methods, including a prescribing claim, for a different purpose and to achieve a different result. Further, these claims would require separate searching and would be separately classified in class 514, subclass 620. Therefore, these claims are independent and distinct from the elected claims and would be a burden of search.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 14-16 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

### *Claim Rejections - 35 USC § 103*

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1, 3 and 9-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maqbool et al (Lancet (1999) 353:897) in view of Mason et al (J. Biol. Chem. (1999) 274:12670-12674).

Maqbool teaches a method of screening for B1 adrenoceptor polymorphisms (see page 897, column 1) comprising:

(a) genotyping the B1 adrenergic receptor of an individual to codon 49 and codon 389 (see page 897, column 1 and figure 1).

With regard to claims 9-11, Maqbool teaches determining whether the patients are homozygous for the presence of Ser49 and Arg389 (see page 897, column 1, "No individual was homozygous for the Gly49 allele").

With regard to claims 1 and 12, Maqbool teaches "The substutition of the positively charged arginine for the neutral glycine residue merits particular attention. This residue is situated at the interface at the interface between transmembrane helix VII and the intracellular tail of the receptor, a highly conserved region critical to G-protein coupling and subsequent cell signalling. An arginine residue is conserved between many species at this position and therefore substitution with a glycine residue

might affect receptor coupling. Since blockade of this receptor prevents myocardial infarction and prolongs life in patients after myocardial infarction or with chronic heart failure, exploring the effects of these gene variants on response to treatment with b-adrenoceptor antagonists and on prognosis would be useful."

This is an express suggestion to predict responsiveness to beta blocker treatment based upon the variation at Ser49.

Maqbool suggests, but does not teach, that the presence of the polymorphisms are indicative of a likely response to a beta blocker medication (see page 897, column 1).

Maqbool does not teach the specific beta blockers of claims 3 or 6, nor does Maqbool directly predict the effects of the polymorphisms.

Mason teaches a method of screening for B1 adrenoceptor polymorphisms (see page 12670, column 2) comprising:

(a) genotyping the B1 adrenergic receptor of an individual to codon 389 (see page abstract and page 12670, column 2)

Mason suggests, but does not teach, that the presence of the polymorphisms are indicative of a likely response to a beta blocker medication (see page 12674, column 1).

With regard to claims 3 and 13, Mason teaches that propranolol is a beta blocker which differentially effects Gly389 and Arg389 (see page 12671, table I).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use genotype the polymorphisms in order to analyze their effect on treatment since Maqbool teaches "Since blockade of this receptor

prevents myocardial infarction and prolongs life in patients after myocardial infarction or with chronic heart failure, exploring the effects of these gene variants on response to treatment with B-adrenoreceptor antagonists and on prognosis would be useful (see page 879, column 1)". Further, Mason teaches "Based on our current results, it might be predicted that individuals bearing the Arg-389 receptor would be most responsive to B-blocker therapy because they would have a genetically determined B1AR that achieves a greater stimulation of adenyl cyclase (see page 12674, column 1)". Thus, Mason expressly predicts and teaches the effect of the codon 389 polymorphism and suggests determining the effect of different antagonists on these gene variants, which is an express suggestion that some variants are more likely to respond to the beta blockers (which are B-adrenoreceptor antagonists) than other variants. Thus, An ordinary practitioner would have expected differential effects of Beta blockers at these two positions.

***Response to Arguments***

5. Applicant's arguments filed December 15, 2003 have been fully considered but they are not persuasive.

Applicant argues that the references do not teach the likelihood of response to beta blockers. This is simply not correct. Mason expressly states "Based on our current results, it might be predicted that individuals bearing the Arg-389 receptor would be most responsive to B-blocker therapy because they would have a genetically determined B1AR that achieves a greater stimulation of adenyl cyclase (see page 12674, column 1)". There can be no clearer statement that the polymorphisms would

be associated than the express statement of prediction. Further, Maqbool expressly teaches that the Ser49 mutation is even more likely to be of significance than the Arg-389 receptor mutation (see column 1). Therefore, the likelihood is taught.

Applicant then argues this is an "obvious to try" situation. The legal standard for "reasonable expectation of success" is provided by caselaw and is summarized in MPEP 2144.08, which notes "obviousness does not require absolute predictability, only a reasonable expectation of success; i.e. , a reasonable expectation of obtaining similar properties. See , e.g. , In re O'Farrell , 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)." In this factual case, there is express suggestion in the prior art of Mason that the method would be PREDICTED to succeed. As Mason states ""Based on our current results, it might be predicted that individuals bearing the Arg-389 receptor would be most responsive to B-blocker therapy because they would have a genetically determined B1AR that achieves a greater stimulation of adenyl cyclase (see page 12674, column 1)". Thus, Masone expressly predicts success. This prediction takes this case beyond the obvious to try situation and creates a reasonable expectation of success There is further evidence as shown in Maqbool that this would be expected to function since Maqbool states "We predict one of these variants is likely to have functional relevance." This sufficient for a reasonable expectation of success. The MPEP cites In re O'Farrell, which notes regarding "obvious to try" at page 1682, that,

> "In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of

> many possible choices is likely to be successful. E.g ., In re Geiger , 815 F.2d at 688, 2 USPQ2d at 1278; Novo Industri A/S v. Travenol Laboratories, Inc ., 677 F.2d 1202, 1208, 215 USPQ 412, 417 (7th Cir. 1982); In re Yates , 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981); In re Antonie , 559 F.2d at 621, 195 USPQ at 8-9. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. In re Dow Chemical Co ., 837 F.2d, 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1985); Hybritech, Inc. v. Monoclonal Antibodies, Inc ., 802 F.2d 1367, 1380, 231 USPQ 81, 90-91 (Fed. Cir. 1 986), cert. denied , 107 S.Ct. 1606 (1987); In re Tomlinson ; 363 F.2d 928, 931, 150 USPQ 623, 626 (CCPA 1966).

The court in O'Farrell then, affirming the rejection, notes " Neither of these situations applies here." For the instant case, it is clear that neither situations applies here either. This is not a situation where the prior art suggests varying a variety of parameters, since the prior art directly points to the use of only two polymorphisms, Ser49 and Arg389. The prior art does not list a number of different polymorphisms and predict success in a huge list. The prior art identifies two particular polymorphisms and both Mason and Maqbool PREDICT success. This is also not a situation where only general guidance was given. The prior art of Mason and Maqbool provides specific guidance directing the use of the Ser49 and Arg389 mutations and their association with beta blocker therapy.

Applicant concludes with an argument of unexpected results. No evidence was presented in either the specification or arguments to support these unexpected results. Further, the specification does not appear to contemplate such an unexpected result, as it states, at page 13, paragraph 46, "'The data provides compelling evidence that the genotype at codon 389 of the B1AR is a strong predictor of blood pressure response to

beta-blocker therapy, and the codon 49 genotype provides additional, information about response." This statement does not suggest that the combination has any unexpectedly better association, nor is such evidence present.

***Conclusion***

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1634